

REMARKS

1. Preliminary Remarks

Claims 1-52 and 54-63 are pending after entry of this amendment. Claims 1-47 and 56-62 were previously withdrawn from consideration. Claims 48-52 and 54-55 were also rejected under 35 U.S.C. §103 as obvious over Minoia *et al.* U.S. Patent No. 5,811,451. Claims 48-52 and 54-55 were rejected under 35 U.S.C. §103 as obvious over Bernstein U.S. Patent No. 4,466,968. Applicant notes with appreciation that the Examiner has withdrawn the previous objection to the specification and the written description rejection based on 35 U.S.C. §112.

Applicant has amended claim 48 to state that the claimed compositions comprise a sub-therapeutic amount of an anti-microbial agent. Applicant makes this amendment solely to expedite prosecution and reserve the right to pursue additional claims, including claims as originally filed, in one or more timely filed continuing applications.

Applicant has also amended claim 48 so that it no longer recites a specific type of microbe causing the microbial infection. This claim element has been removed from independent claim 48, but is included in dependent claim 63, which is newly presented by this amendment.

2. Claims 48-52 and 54-55 Are Not Obvious In View of Minoia *et al.* or Bernstein

The Office Action rejected claims 48-52 and 54-55 under 35 U.S.C. §103 as obvious over Minoia *et al.* U.S. Patent No. 5,811,451. Claims 48-52 and 54-55 were rejected under 35 U.S.C. §103 as obvious over Bernstein U.S. Patent No. 4,466,968.

Applicant submits that the subject matter of claims 48-52 and 54-55 is not disclosed or suggested by Minoia *et al.* or Bernstein. The Office Action incorrectly concludes that one of ordinary skill in the art would have modified the teachings of Minoia *et al.* or Bernstein. There is no motivation or suggestion in the art to modify those references in the manner suggested by the Office Action. Neither Minoia *et al.* nor Bernstein discloses or suggests a composition comprising a) an opioid inhibitor of an ABC transporter; and b) an anti-microbial agent.

Nonetheless, in an effort to expedite prosecution, Applicant has amended independent claim 48 so that it states that the composition comprises a sub-therapeutic amount of an antimicrobial agent. This amendment is supported throughout the specification, including, for example, at paragraphs 0015, 0016, 0020, 0041, and 0171. The specification teaches that the efficacy of antimicrobial agents can be enhanced by co-administering the antimicrobial agent with an ABC transporter inhibitor. (See, e.g., page 9, lines 12 to 14). For example, the specification states, "The invention provides methods of suppressing growth of a microbe expressing an ABC drug transporter protein comprising by contacting the microbe with a sub-therapeutic amount of an antimicrobial agent in the presence of an opioid inhibitor of the ABC drug transporter."

Neither Minoia nor Bernstein teaches or suggests a composition comprising a sub-therapeutic amount of an antimicrobial agent combined with an opioid inhibitor of an ABC drug transporter. As mentioned above, neither reference discloses a composition containing both compounds. Moreover, neither Minoia nor Bernstein discloses that the amount of the antimicrobial agent can be a sub-therapeutic amount.

Minoia generally relates to the treatment of endorphin-mediated pathologies with opiate antagonists and calcium salts. (See Title). Minoia only briefly describes the use of antibiotics, in Example 5 of the specification. Minoia states that animals affected by distemper were treated with "antibiotics (cephalosporins+aminoglycosides i.m. for 1 week." (see Example 5, col. 6, lines 18-25). Nothing in Minoia discloses, suggests or enables the use of a sub-therapeutic amount.

Bernstein generally relates to preventing or treating nausea and vomiting. Bernstein discloses that naloxone or a chemical similar narcotic antagonist is administered either to prevent nausea and/or vomiting or to treat such symptoms. (col. 2, lines 23-26). One of the causes of nausea and/or vomiting identified by Bernstein is "high dose oral antibiotic therapy", along with viral or bacterial gastroenteritis and alcohol ingestion. (col. 2, lines 26-36). For example, Bernstein discloses the use of 2 grams of erythromycin and 1 gram of tetracycline hydrochloride. (col. 4, lines 22 and 38). Bernstein does not disclose or suggest a sub-therapeutic amount of an antimicrobial agent. In fact, by referring to "high dose oral antibiotic therapy", Bernstein teaches away from the use of a sub-therapeutic amount of an antimicrobial agent.

Accordingly, Applicant submits that claim 48 as amended (as well as dependent claims 49-52, 54-55 and 63) are not obvious over Minoia *et al.* or Bernstein and that the obviousness rejection may properly be withdrawn.

3. Claims 48-52 And 54-55 Are Not Indefinite

The Office Action of March 31, 2005 entered a new ground of rejection. The Office Action stated that claims 48-52 and 54-55 were indefinite under 35 U.S.C. §112, second paragraph. The Office Action stated that claim 48 recites the limitation “wherein the microbe causing the microbial infection is . . .”, and there is insufficient basis for this limitation. The Office Action also stated that claim 48 recited alternative limitations that are improperly expressed.

Applicant has amended claim 48 to remove the objected-to language. This amendment does not narrow the claim, but rather broadens it. Applicant had amended claim 48 to include the objected-to language in an attempt to overcome the obviousness rejection. In view of the Office Actions statement that this amendment does not add to applicant's response and does not result in a structural difference between the claimed composition and the prior art composition, Applicant is removing the objected-to language.

Applicant has added claim 63, which recites that the antimicrobial agent is adapted to inhibit a microbe selected from *Staphylococcus*, *Streptococcus*, *Micrococcus*, *Peptococcus*, *Peptostreptococcus*, *Enterococcus*, *Bacillus*, *Clostridium*, *Lactobacillus*, *Listeria*, *Erysipelothrix*, *Propionibacterium*, *Eubacterium*, *Corynebacterium*, *Pseudomonas*, *Plasmodium*, *Leishmania*, *Absidia*, *Aspergillus*, *Basidiobolus*, *Blastomyces*, *Candida*, *Coccidioides*, *Conidiobolus*, *Cryptococcus*, *Cunninghamella*, *Histoplasma*, *Mortierella*, *Mucor*, *Paracoccidioides*, *Rhizopus*, *Saksenaea*, , *Acidaminococcus*, *Acinetobacter*, *Aeromonas*, *Alcaligenes*, *Bacteroides*, *Bordetella*, *Branhamella*, *Brucella*, *Calymmatobacterium*, *Campylobacter*, *Cardiobacterium*, *Chromobacterium*, *Citrobacter*, *Edwardsiella*, *Enterobacter*, *Escherichia*, *Flavobacterium*, *Francisella*, *Fusobacterium*, *Haemophilus*, *Klebsiella*, *Legionella*, *Moraxella*, *Morganella*, *Neisseria*, *Pasturella*, *Plesiomonas*, *Proteus*, *Providencia*, *Pseudomonas*, *Salmonella*, *Serratia*, *Shigella*, *Streptobacillus*, *Veillonella*,

Vibrio, or *Yersinia*. Applicant submits that the grounds of indefiniteness recited in the Office Action dated March 31, 2005 are not applicable to new claim 63.

4. The Drawings Have Been Corrected

Applicant is submitting a corrected drawing sheet for Figure 1 and amending claim 51 to correct an obvious typographical error. The drawing is being corrected to reflect that there should not be a double bond between C7 and C8 for nalmeffene, naltrexone, naloxone, or 6- β -naltrexol. Claim 51 is also being amended so that the structure does not require a double bond between C7 and C8. The amendments do not add new matter, since the corrected chemical structures are supported by the disclosure of the chemical names.

5. Conclusion

For the foregoing reasons, Applicant submits that the amended claims comply with the written description requirement and are not rendered obvious by Minoia *et al.* or Bernstein. Thus, claims 48-52, 54-55 and 63 are in condition for allowance. The Examiner is invited to telephone Applicant's representative to discuss any questions or if Applicant's representative may be of any assistance to the Examiner in the reconsideration and allowance of this case.

Please charge any fees incurred in connection with this submission to Deposit Account No. 13-0017 in the name of McAndrews, Held & Malloy, Ltd.

Respectfully submitted,



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Dated: September 29, 2005

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